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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,293	01/09/2001	Thomas E. Wagner	035879-0116	5976

22428 7590 07/03/2003

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EXAMINER

LI, QIAN J

ART UNIT PAPER NUMBER

1632

DATE MAILED: 07/03/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/756,293

Applicant(s)

WAGNER ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 January 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/03 has been entered.

Claims 1-15 and 17-31 have been canceled. Claims 32-44 are newly submitted.

In view of the amendments, previous rejections have been modified and new grounds of rejection are necessitated. Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #16 would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 32 is objected to because claim recitation "populations" in line 5 should be in singular form.

Claim 42 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, claim 42 depends from claim 34 and recites, "wherein said method is used for treatment of an

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autoimmune disease". However, claim 34 is a method for making a cell fusion product, it is the product but not the method of making such that could be used for treatment.

Further, if applicants intend to claim a method for treatment of an autoimmune disease, then the claim is drawn to a non-elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-34 are rejected under 35 U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to specify the terms "first marker" and "second marker" as now claimed. The terms "first marker" and "second marker" are now considered to be new matter. Moreover, claim 33 encompasses a hybrid cell fused between an APC and a cell infected with a pathogenic organism. The original disclosure fails to specify a cell population infected with a pathogenic organism. The subject matter is now considered to be new matter.

The specification as originally filed fails to describe "the first marker" and "second marker", it only describes "a selectable marker" as *"gene products which render the cell resistant to specific cell toxins or allow them to grow under certain metabolic conditions"* (page 3, lines 26-28), and the specification goes on to teach, *"Since the introduction and*

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selection schemes using markers requires culture and multiple cell division, they cannot be applied to dendritic cells, because DCs are terminally differentiated, non-dividing cells" (paragraph bridging pages 3 and 4). Since the new claims clearly require that cell sorting does not involve antibiotic or metabolic selection, the original defined "selectable marker" is clearly distinct from the markers recited in the current claims, and the specification teaches away from using those originally specified markers, thus, the new claims introduce new matter into the disclosure.

The specification as originally filed fails to specify a hybrid cell fused between a DC and a pathogen-infected cell as now claimed in claim 33. In paper #16, applicants pointed to the support for new claim 33 in page 13, lines 25-28. However, the cited paragraph teaches hybrid cells fused between APC and cells *isolated* from the pathogenic organism. The specification as originally filed fails to describe the subject matter as now claimed, thus, the new claim introduces new matter into the disclosure.

MPEP 2163.06 notes, "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". 37 CFR 1.118 states: ALL AMENDMENT TO THE SPECIFICATION, INCLUDING

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THE CLAIMS AND THE DRAWINGS FILED AFTER THE FILING DATE OF THE APPLICATION MUST CONFORM TO AT LEAST ONE OF THEM AS IT WAS AT THE TIME OF THE FILING OF THE APPLICATION. MATTER NOT FOUND IN EITHER, INVOLVING A DEPARTURE FROM OR AN ADDITION TO THE ORIGINAL DISCLOSURE, CANNOT BE ADDED TO THE APPLICATION AFTER ITS FILING DATE EVEN THOUGH SUPPORTED BY AN OATH OR DECLARATION IN ACCORDANCE WITH 37 CFR 1.63 OR 37 CFR 1.67 FILED AFTER THE FILING DATE OF THE APPLICATION.

Applicant is required to cancel the new matter in the reply to this Office Action.

To the extent that the claimed markers and methods are not described in the instant disclosure, claims 32-43 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Claims 32-36, and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in

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terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement*; Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims recite "a first marker" and "a second marker", and using such for cell sorting. Given the broadest reasonable interpretation, the claims embrace a genus of molecules that could be used as markers for hybrid cell sorting, and any method for sorting the markers. However, the only marker family disclosed in the specification is fluorescent dyes, and the only sorting method is the fluorescence activated cell sorting. The specification fails to describe the genus of the first and second markers, or the various methods for sorting these markers, the specification has not set forth in terms of structural or distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed genus of the invention.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly

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states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of molecules that could serve as the first and second markers. Therefore, only the described fluorescent dyes meet the written description provision of 35 U.S.C. §112, first paragraph.

To the extent that the claimed markers and methods of sorting such markers are not described in the instant disclosure, claims 32-36 and 39-43 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

In paper # 16, applicants argue that a person of ordinary skill in the art, using techniques that are well known, would be able to sort hybrid cells without using fluorescent dye staining and metabolic selection. Applicants particularly point to the combination of flow cytometry using magnetic microbeads or measurement of optical properties related to cell size or density.

The argument has been carefully considered but found not persuasive. This is because claims embrace fusing any antigen presenting cell with not only any tumor cell, but also any pathogenic organism, and any target cell, these fusion partners vary significantly in size and intracellular density, and the specification is silent concerning the sizes and cell densities of various types of fusion partners, and how to use these conventional cell-sorting methods for separating different cell populations. For example, the sizes and intracellular densities of tumor cells may vary significantly depending on the types of the tumor cells. The size and intracellular density may not change to a degree that one can identify the fusions from the starting dendritic cells when the fusion partner is a microorganism. Cell sorting with magnetic microbeads requires coating the beads with antibodies against a cell marker, the specification fails to teach any marker for target cells of autoimmune diseases, any marker from a cell of a microorganism, and whether and how to preserve the diversity of hybrid cells so that they express selectable markers. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991), and 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the

scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Accordingly, the instant specification fails to provide an enabling disclosure to support the full scope of the invention. Applicants are reminded that the Federal Circuit has stated that:

a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

The rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. If there is no disclosure of starting materials and of conditions under which the process can be carried out, undue experimentation is required. Failure to provide such teachings cannot be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims recite that "the *diversity* of the starting cell populations is preserved in the resultant hybrid cell population" for the broadly claimed various type of hybrid cells, however, the specification is silent and fails to teach what the term encompasses and

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how such diversity be preserved. Considering the broadly claimed fusion partners, such as a microorganism, whose antigenic epitope is not necessarily expressed on the surface of a cell; in the case of autoimmune disease, the target of the autoantibody in systemic lupus erythematosus is intracellular antigens, such as chromatin, thus, the antigenic epitope is not present in cell surface. In the case of a tumor vaccine, tumorigenic proliferation is one of the characteristics of the starting tumor cell population, it is unclear whether the hybrid cells between the DC and tumor cell include or exclude such a trait of the starting cell population; and if the answer is positive, the recited product is then not suitable for use as a vaccine. In view of such, the specification fails to provide an enabling disclosure commensurate with what is now claimed.

Claim 33 is drawn to fusion between an antigen presenting cell and a pathogenic organism, the later encompasses any eukaryotic and prokaryotic organism ranging from viruses, Chlamydia, to bacteria and parasites. However, the specification fails to teach how to conduct labeling and cell fusion between an APC and a cell isolated from a pathogenic organism. For example, whether a fluorescent dye would stain a virus or bacteria. Interestingly, most of the microorganisms are intracellular pathogens, when in contact with a mammalian cell, they infect the cell by entering and replicating inside the cell. To this end, the specification is completely silent with regard to fusing a prokaryotic microorganism with a eukaryotic cell, thus, fails to provide an enabling disclosure to support the full scope of the claims. Moreover, although a hybrid cell derived from the fusion between an APC and a cell infected with a pathogenic organism could be made,

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it is unpredictable whether such hybrid cells could be used as vaccine for treating a related disorder. This is because the cells infected by the organism do not necessarily express an immunogenic antigen on its surface that stimulates an immune response, and the immune response generated from pathogen-infected cells does not always protect the host. Taking *Chlamydia* as an example, *Kim et al* (J Immunol 1999 Jun;162:6855-66) teaches "LITTLE IS KNOWN ABOUT WHETHER CHLAMYDIAL GENITAL TRACT INFECTION IN HUMANS INDUCES ANY DEGREE OF PROTECTIVE IMMUNITY AGAINST REINFECTION." (See page 6855, left column). They go on to teach past infections of humans with Ct may confer partial protection against subsequent infections, however, the induction of CTL responses in human *chlamydial* infection has not been reported, and their potential role in immune protection is unassessed (See page 6856, left column). Furthermore, they individually evaluate several major outer membrane proteins that would induce CTL in certain cells from different patients. They teach in the discussion that "APC UTILIZED IN STUDIES WITH MICE MIGHT HAVE RESULTED IN IMMUNOLOGICAL EVENTS THAT ARE DISTINCT FROM THOSE TRIGGERED BY APCs PRESENT IN HUMAN GENITAL TRACT", that "NONE OF THESE STUDIES WITH MICE IDENTIFIED THE CT AGS RECOGNIZED BY PROTECTIVE CTLs." "FURTHER INVESTIGATIONS ARE NEEDED TO DEFINE MECHANISMS BY WHICH CTLs MIGHT PROTECT AGAINST CT AND TO EXAMINE WHETHER CTLs ARE IN PART RESPONSIBLE FOR IMMUNOPATHOLOGY". Indeed, one of the important mechanism that many viruses cause host tissue damage is not by the infection itself, but by the host cell destruction via a host immune response against the intracellular virus, such as hepatitis virus and herpes simplex virus. Thus, even though the hybrid cell could be made, the specification fails to provide an enabling

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disclosure for the breadth of the claims drawn to a vaccine for treating any and all disease associated with a pathogenic organism. The specification fails to provide an enabled disclosure commensurate to its scope as the claims are drawn to making a therapeutic agent that could induce a protective immunity.

Claim 34 is drawn to fusion between a population of target cells and an APC deficient in an accessory interaction. However, the specification fails to specify such target cell population, the markers that could be used for cell sorting, and how to make a dendritic cell that lacks an accessory interaction. For example, a hybrid cell derived from a tumor cell and a resting DC or a premature B cell lacks a B7 accessory molecule, however, the accessory molecule would be expressed upon later antigen stimulation and activation. Thus, the specification fails to teach a DC permanently lacking an accessory molecule other than a fibroblast. Tuning into the state of the art in autoimmunity, autoantigens responsible for a particular disease is either not clearly defined or not limited to one particular cell population, or can be easily isolated. Even if a particular cell population is known as the target of the immune response, the complex nature of initiation and sustaining an autoimmune disease made it impossible to determine whether the hybrid cell alone could prevent or avert an autoimmune disease. For example, *Zhou et al* (J Immunol 2001;167:7126-33) teach that specific autoantigen genes are selectively overexpressed in scleroderma *fibroblasts* in autoimmune systemic sclerosis, however, such auto-antigen expressing fibroblast cells have not induce tolerance in these patients. Apparently although the principle of inducing tolerance is well known in the art, effective immune regulation is much more complicated than the

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principle, and the report of prevention or treatment of such disease in the field is rare.

According to *Kalden et al*, "EVEN RELATIVELY "SIMPLE" EXPERIMENTAL MODELS OF AUTOIMMUNITY REMAIN DIFFICULT TO TREAT", AND "THE EXPERIMENTAL MODELS OF AUTOIMMUNE DISEASES ARE CLEARLY DISTINCT DISORDERS OF HIGHLY STRUCTURED AUTOIMMUNITY; DESPITE THE FACT THAT THEY SHARE SOME IMMUNOPATHOGENETIC PATHWAYS, THEY RELY ON QUITE DIFFERENT POLYGENETIC BACKGROUNDS. THUS, THE BENEFICIAL EFFECTS OF A CERTAIN TREATMENT IN ONE MODEL CANNOT NECESSARILY BE EXTRAPOLATED TO ANOTHER" (*Kalden et al. (1998) Advances in Immunology*, 68; pages 333-395, paragraph 2 through page 396 paragraph 4).

Thompson et al (*Immunol Cell Bio* 2002;80:509-19) discuss multiple pathways that dendritic cells could influence the T cell decision between tolerance and immunity. In a post filing date, they teach, "THE MOLECULAR AND CELLULAR BASIS OF THESE CONTROLS IS BEING UNDERSTOOD AT AN INCREASINGLY MORE COMPLEX LEVEL (abstract), "AN INTENSIVE SEARCH IS UNDERWAY GLOBALLY FOR OTHER PATHWAYS. FURTHERMORE, EVIDENCE IS EMERGING THAT ONE PATHWAY MIGHT INDUCE A SECOND PATHWAY, THROUGH A TYPE OF DOMINO EFFECT, ... EXACTLY HOW THESE PATHWAYS IMPACT ON T CELL AND DC REGULATORY FUNCTION AND IN WHICH SITUATIONS A PARTICULAR MECHANISM WILL PREDOMINATE REMAINS TO BE SEEN" (right column, page 514). Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Again, the rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. However, if there is no disclosure of starting materials and of conditions under which the process can be carried out, undue experimentation is required. Failure to provide such teachings cannot

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be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC, 1997). Although the instant specification provides a brief review of the strategy for fusion between an APC and cells other than a tumor cell, it is not enabled for its full scope because the specification fails to provide an enabling disclosure for these aspects of the invention as discussed in detail *supra*, and determination of the therapeutic effects of the resultant hybrid cell is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving fusion for any pathogen and any target cell of an autoimmune disease, in particular for the prevention and treatment of any and all infectious and autoimmune diseases, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to making fusions between eukaryotic and prokaryotic cells, and the breadth of the claims directed to making numerous therapeutic effective vaccines, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because claims as written do not make clear whether the first and second dye are the same or different, the standards for cell sorting, and the correlation between the first and second dye (or marker) of steps (a) and (b), and the cell sorting process in step (d), so that the standard of the cell sorting is unclear, and the metes and bounds of the claims are uncertain.

Claims are vague and indefinite because of the limitation, "the *diversity* of the starting cell populations is preserved in the resultant hybrid cell population". The specification fails to define the term, it is unclear what the term encompasses or excludes, and thus, the metes and bounds of the claims are uncertain.

Claim 33 recites the limitation, "said affected cells" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 recites the limitation, "said pharmaceutically acceptable vehicle". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32, 35-38, 41, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Gong et al* (Nature 1997;3:558-561, IDS), in view *Koolwijk et al* (Hybridoma 1988;7:217-225).

Claims are drawn to a method for preparing tumor vaccine composition comprising contacting a tumor cell population with a first dye, and a dendritic cell population with a second dye, fusing the two population with one another, and purifying the resultant hybrid cell by cell sorting (for double-stained cells) such as FACS, and suspending the resultant hybrid cell population in a pharmaceutically acceptable buffer, wherein said cell sorting does not involve antibiotic or metabolic selection and the diversity of the starting cell populations is preserved in the resultant hybrid cell population, wherein the resultant cell population contains less than 5-10% non-hybrid starting cells, wherein the pharmaceutically acceptable buffer is normal saline.

Gong et al teach a method for preparing a tumor vaccine comprising fusion between dendritic cells and MC38/MUC1 tumor cells, they bring the two different types of cells into contact and fusing with PEG, and the resultant hybrids possess both DC (fig. 1a) and tumor cell surface markers (capable of inducing specific anti-tumor response). They suspend the hybrid cell in PBS and using such as tumor vaccine

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(figure 2). For the hybrid cell selection, *Gong et al* use HAT plating, (metabolic selection) or plain plating followed by separation according to the strength of cell attachment to the culture dish. They then sort the cells by FACS using FITC fluorescent dye (paragraph bridging pages 560-1) and selecting according to cell surface markers (fig. 1a). Although *Gong et al* do not specify the purity of the resultant cell population with regard to the contents of the starting cell population, the multiple marker selection with FACS gating would result in a highly purified population because only cells positive for a certain marker would travel through the gate. *Gong et al* fail to teach selecting hybrid cells with two different fluorescent dyes.

Koolwijk et al teach a method of preparing and purifying a hybrid cell, comprising contacting a first cell with a green fluorescent, contacting a second cell with a red fluorescent, bringing the two different cells into contact and fusing the cells with polyethylene glycol 4000, wherein the fusion hybrids secrete both antibodies that each of the starting cell population secretes (anti-horseradish peroxidase and human IgA1, abstract). The double fluorescent stained hybrid cells were then sorted by FACS (e.g. abstract). *Koolwijk et al* also teach enriching (purifying) the fused cell population by Percoll density gradient centrifugation (1st paragraph, page 218). *Koolwijk et al* go on to teach, "THE MAJOR ADVANTAGE OF THIS METHOD OF HYBRID HYBRIDOMA ISOLATION OVER THE METHOD USING MUTANT PHENOTYPES AND A BIOCHEMICAL SELECTION AFTER FUSION IS THE FAST ISOLATION PROCEDURE. NO TIME-CONSUMING ISOLATION OF THE MUTANT PHENOTYPES BEFORE FUSION IS NEEDED. AFTER FUSION, THE BIOCHEMICAL SELECTION PROCEDURE IS NOT NECESSARY" (see Introduction and Discussion). The fusion partner cells used by *Koolwijk et al* are

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different hybridoma cells, which are the fusion product of tumor cells and B-lymphocytes (a type of antigen presenting cells). *Koolwijk et al* do not teach fusing APC and tumor cell for making a vaccine.

Evidently, fusing tumor cells and dendritic cells to make a vaccine composition for anti-tumor effect is well-known in the art as taught by *Gong et al*, selecting and purifying hybrid cells using different dyes is also well known in the art as taught by *Koolwijk et al*. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods taught by *Koolwijk et al*, in the process for selection and purification of dendritic-tumor cell hybrids as taught by *Gong et al* with a reasonable expectation of success. Even if the resultant hybrid cells taught by *Gong et al* are not 95% pure, *Koolwijk et al* has illustrated the motivation and approach to purify the fused cell population. As for the pharmaceutical acceptable buffer, *Gong et al* use PBS, not NS. However, both PBS and NS are well known in the art as alternatives for pharmaceutical acceptable carrier. The ordinary skilled artisan would have been motivated to modify the method because the double fluorescent cell sorting requires fewer steps and less time for making and selecting hybrid cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In paper No. 16, applicants argue that a feature of the present invention is that the heterogeneity/diversity of the starting cell population is preserved in the hybrid cells, whereas "a person of ordinary skill in the art would know that the method of *Gong et al* does not maintain the diversity of starting cell subpopulations".

In response, applicants' assertion is in error. As discussed *supra*, *Gong et al* clearly teach, "THE PRESENT STUDIES HAVE PURSUED AN ALTERNATIVE DC-BASED STRATEGY FOR INDUCING IMMUNITY AGAINST KNOWN OR UNIDENTIFIABLE TUMOR ANTIGENS" (right column, page 558), and the hybrid cells expressing DC marker, such as MHC class II (fig. 1a). Obviously, *Gong et al* teach that the heterogeneity of the starting cell population is preserved for cancer vaccine. In fact, *Koolwijk et al* specifically teach making a hybrid cell so that it possesses diverse characteristics of both of the starting population, i.e. a B cell hybridoma secreting an antibody having the specificities of both of the starting cell populations.

For reasons of record and those set forth foregoing, the rejection stands.

Conclusion

No claim is allowed.

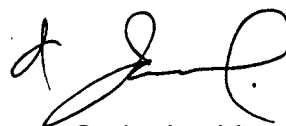
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Examiner
Art Unit 1632

QJL
June 30, 2003